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Reappraisal of Evidence of Microscopic Portal Vein Involvement by Hepatocellular Carcinoma Cells with Stratification of Tumor Size

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Abstract

Background Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death internationally, it is necessary to reappraise evidences of HCC cells involving the portal vein, especially considering tumor size.

Materials and methods Histopathological evidence and dynamic evidences of radiology and cytology from publication were collected and analyzed.

Results Frequencies of microscopic portal vein involvement (MPVI) and microscopic intrahepatic metastasis (MIM) in resected specimens with single nodule HCC were lower than that of multi nodule HCC, although not significantly. Early HCC ($\leq$1.5 cm) was with extremely low to 0 frequencies of MPVI and MIM. HCC >5 cm showed a tendency of flowing HCC cells into portal vein, which was coincident with significantly high frequency (64.1 %) of MPVI for HCC >5 cm. There were no significant difference of frequencies of MPVI and MIM between groups of tumor $\leq$2, $\leq$3, and $\leq$5 cm.

Conclusions Single nodule HCC >5 cm needs anatomic resection and the root of portal vein should be firstly ligated because of tendency of flowing HCC cells into portal vein. For single nodule HCC $\leq$2 cm, there was a risk of about 16.2 % of MPVI, and a risk of about 16.2–26.4 % of MPVI for those single nodule HCC $\leq$5 cm, however, there was a risk of extremely low to 0 of MPVI for early HCC ($\leq$1.5 cm). Surgeons have to balance liver reserve and risk of MPVI for HCC $\leq$5 cm before deciding anatomic or nonanatomic resection.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death internationally [1]. It was internationally estimated for the year 2000 that HCC was the fifth most common cancer in men and the eighth most common cancer in women [2]. Eastern Asia, Middle Africa, and some countries of Western Africa are the areas with highest risk of HCC prevalence. Patients with HCC showed an overall population-based 1- and 3-year survival of 20 and 5 % respectively, which was unsatisfying, however, 5-year survival of patients with resectable HCC ranged widely from 35 to 70 % according to literature [3–8].

Although there are kinds of treatment modalities for HCC, hepatic resection is a widely accepted treatment modality for HCC. Hepatic resection is an aggressive treatment for selected HCC patients, and only which can provide potentially curative options for HCC [9–11].There were lots of clinical analysis considering the outcome between nonanatomic and anatomic resection based on Couinaud's segments of liver anatomy since 1980s, attempting to provide clinical evidences of whether nonanatomic and anatomic resection showed superiority, however, the result remains controversial.

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One may be curious, if there is any supportive theory for the performance of anatomic resection for HCC, because nonanatomic or limited resection can be performed not so technically demanded and can contribute to more liver remnant reservation. The supportive theory should be the following 3 points: 1. Couinaud's portal segments of liver anatomy; 2. HCC cells tend to invade the portal vein, tumor subsequently spread into the regional hepatic regions and result in satellite nodules, anatomic resection can eradicate venous tumor thrombi present within the anatomically resected domain [12, 13]; 3. Microscopic vascular invasion is a strong predictor of outcome following hepatic resection and liver transplantation of HCC [14–17]. Couinaud's portal segments of liver anatomy and microscopic vascular invasion as strong prognostic predictors are now globally accepted.

That HCC cells tend to invade the portal vein or have high frequent invasion to portal vein was gradually present in literature since early 1980s. In 1983, Makuuchi M. et al. [12] reported that microscopic tumor thrombus in the portal venous branch was found in 73 % of 62 patients with HCC less than 5 cm, which seems the first description of frequency of HCC cells invading portal vein. Although there were similar reports subsequently, most of which did not aim to focus on frequency of HCC cells invading portal vein. Moreover, thanks to the development of imaging modality, biomarkers, and surveillance guideline, more and smaller HCC with early stage can be detected [18–21]. Then how often do HCC cells invade portal vein, especially for HCC with smaller size? Therefore, it is necessary to reappraise evidences of HCC cells involving the portal vein, especially considering tumor size.

Materials and methods

Methods of evidence acquisition and data sources

In order to revisit and reappraise evidences of HCC cells invading the portal vein, the following evidence acquisitions were applied. The first acquisition was the frequency of microscopic portal vein involvement (MPVI, including portal vein invasion and portal vein tumor thrombus) and microscopic intrahepatic metastasis (MIM) in resected specimens and attention was paid to tumor size, which is histopathological evidence. The second acquisition was radiology and cytology evidence regarding tumor to the associated portal vein, which is dynamic evidence.

Studies were identified by searching MEDLINE and PubMed databases for articles with keywords "portal invasion and HCC", "anatomic resection and HCC", "anatomical resection and HCC", "systematic hepatectomy and HCC", "segmentation resection and HCC", Additional papers and book chapters were identified by a manual search of references from reviewed articles.

Statistics

Data were presented as mean ± S.D. values. For statistical analyses, Student's *t* test was used to compare data between single nodule and multi nodule. If data were not of normality with tests for normality, Wilcoxon two-sample test was applied. Spearman's correlation coefficient analysis was used for identifying correlation between MPVI and MIM in resected specimens. ANOVA was applied for analyzing difference between groups of different tumor sizes. Significance levels of $p < 0.05$ were considered as statistically significant.

Results

A total of 409 literatures were found, and literatures of recurrence HCC, macroscopic vascular invasion, only microscopic vascular invasion that including portal and hepatic veins were excluded. For the first acquisition of histopathological evidence, 70 literatures regarding portal vein involvement and/or micrometastasis were identified, from which 65 series were used for statistics (Table 1) [22–68]. There were 3 literatures of radiology and 2 literatures of cytology of dynamic evidences.

Frequencies of MPVI and MIM in resected specimens

There were 58/65 (89.2 %) series with consecutive cases in patient collection. The consecutive period of each series ranged from 2–21 years (12.3 ± 5.3); the case number of each series ranged from 5–1,139 cases (169.5 ± 193).

Frequency of MPVI in resected specimens of each series was (26.4 ± 17.3) %, ranging from 0–73 %, and frequency of MIM in resected specimens of each series was (21.5 ± 16.5) %, ranging from 0–66.7 %.There were 5 series (110 cases) with tumors ≤1.5 cm and single nodule (early HCC), frequency of MPVI in resected specimens was 0.5 % (3 of 4 series were 0), and frequency of MIM was 0.

Spearman's correlation coefficient analysis revealed that, among 22 series with both data of MPVI and MIM, there was significant correlation between MPVI and MIM in resected specimens, the coefficient was 0.60, $p = 0.0035$ (Fig. 1).

When the data was stratified by single nodule or multi nodules, frequency of MPVI in resected specimens with single nodule of each series was (21.6 ± 17) %, ranging from 0–64.1 %, however, frequency of MPVI in resected specimens with multi nodules of each series was (28.5 ± 12.8) %, ranging from 7.1–48.2 %, and there was

Table 1 Frequencies of MPVI and MIM in resected specimens

Authors	Research period (years)	Case number (n)	Frequency of MPVI	Frequency of MIM	Tumor size (cm)	Single nodule	Publication year
Okamoto E et al.	NS	34	50 % (17/34)	44.1 % (15/34)	≤3	1	1987
Okamoto E et al.	NS	34	20 %	20 %	≤2	1	1987
Shirabe K et al.	1976–1988 (13)	50	16 % (8/50)	22 % (11/50)	≤3	1	1991
Hsu HC et al.	1979–1983 (5)	44	18.2 % (8/44)	36.6 % (16/44)	≤5	0	1985
Hsu HC et al.	1979–1983 (5)	39	64.1 % (25/39)	66.7 % (26/39)	>5	1	1985
Makuuchi M et al.	NS	62	73 %	NS	≤5	NS	1983
Kanai T et al.	1978–1985 (8)	61	27.9 % (17/61)	23 % (14/61)	≤3	0	1987
Kanai T et al.	1978–1985 (8)	5	0 (0/5)	0 (0/5)	<1.2	1	1987
Ercolani G et al.	1983–1999 (17)	224	46. 9 % (105/224)	NS	NS	0	2003
Wakasa K et al.	NS	28	25 % (7/28)	0 (0/28)	≤5	0	1985
Wakasa K et al.	NS	14	7.1 % (1/14)	0 (0/28)	≤2	0	1985
Adachi E et al.	1976–1992 (17)	97	18.4 % (21/114)	NS	≤3	NS	1996
Adachi E et al.	1976–1992 (17)	232	64.4 % (76/118)	NS	>3	NS	1996
Kang CM et al.	1998–2005 (8)	167	14.4 % (24/167)	4.8 % (8/167)	≤4	1	2010
Yamamoto J et al.	1984–1991 (8)	386	48.2 % (186/386)	NS	NS	0	1996
Yamanaka N et al.	1986–1987 (2)	31	29 % (9/31)	41.9 % (13/31)	NS	NS	1992
Ueno S et al.	1990–2004 (15)	116	23.3 % (27/116)	NS	≤3	0	2008
Yamamoto M et al.	1990–1994 (5)	204	NS	19.1 % (39/204)	≤5	1	2001
Fuster J et al.	1989–1994 (6)	48	NS	25 % (12/48)	<5	1	1996
Regimbeau JM et al.	1990–1996 (7)	64	NS	37.5 % (24/64)	≤4	1	2002
Tanaka K et al.	1992–2005 (14)	125	NS	31.2 % (39/125)	NS	1	2008
Dahiya D et al.	1983–2002 (20)	373	NS	18.5 % (69/373)	≤5	1	2010
Nakashima Y et al.	1992–2003 (12)	22	0	0	≤1.36	1	2003
Nakashima Y et al.	1992–2003 (12)	187	29.41 % (55/187)	11.76 % (22/187)	<3, >1.36	1	2003
Takayama T et al.	1982–1991 (10)	15	NS	0	≤1.4	1	1998
Takayama T et al.	1982–1991 (10)	65	NS	21 % (11/52)	≤2	1	1998
Kojiro M	NS	50	2 % (1/50)	0	≤1.17	1	2005
Kojiro M	NS	82	22 % (18/82)	9.6 %	≤2, >1.17	1	2005
Lai EC et al.	1972–1988 (17)	117	NS	35 % (41/117)	NS	NS	1990
Okusaka T et al.	1992–1999 (8)	18	0	0	NS (Early HCC)	1	2002
Okusaka T et al.	1992–1999 (8)	131	21.4 % (28/131)	NS	≤3	1	2002
Kubo S et al.	1991–2003 (13)	61	6.6 % (4/61)	NS	≤2	1	2003
Kubo S et al.	1993–2006 (14)	24	45.8 % (11/24)	NS	NS	1	2007
Hasegawa K et al.	1994–2001 (8)	201	NS	31.9 % (67/210)	NS	1	2005
Roayaie S et al.	1990–2009 (20)	132	NS	12.1 % (16/132)	≤2	1	2013
Shindoh J et al.	1994–2008 (15)	280	NS	8.57 % (24/280)	≤5	1	2013
Ochiai T et al.	1987–2002 (16)	305	NS	26.2 % (80/305)	NS	0	2007
Imamura H et al.	1990–1998 (9)	249	NS	16.1 % (40/249)	≤5	0	2003
Sasaki A et al.	1982–2003 (22)	235	46.8 % (110/235)	NS	NS	0	2006
Chiappa A et al.	1993–1997 ((5)	51	NS	27.5 % (14/51)	NS	0	2000
Kobayashi A et al.	1990–2004 (15)	224	29.9 % (67/224)	NS	NS	1	2008
Kamiyama T et al.	1997–2009 (13)	521	25.7 % (134/521)	NS	NS	0	2012
Shirabe K et al.	1992–2005 (14)	267	20.6 % (55/267)	NS	NS	0	2009
Kamiyama T et al.	1990–2006 (17)	287	11.8 % (34/287)	6.3 % (18/287)	≤5	1	2010
Kamiyama T et al.	1990–2006 (17)	35	17.1 % (6/35)	62.9 % (22/35)	≤3	0	2010
Nanashima A et al.	1990–2008 (19)	201	16.4 % (33/201)	NS	NS	1	2010
Nanashima A et al.	1990–2008 (19)	70	38.6 % (27/70)	NS	NS	0	2010
Nanashima A et al.	1990–2008 (19)	62	3.2 % (2/62)	NS	<2	NS	2010

Table 1 continued

Authors	Research period (years)	Case number (n)	Frequency of MPVI	Frequency of MIM	Tumor size (cm)	Single nodule	Publication year
Nanashima A et al.	1990–2008 (19)	123	22 % (27/123)	NS	≥2, ≤5	NS	2010
Nanashima A et al.	1990–2008 (19)	86	34.9 % (30/86)	NS	>5	NS	2010
Sawada T et al.	2000–2008 (9)	46	NS	6.5 % (3/46)	≤2	1	2011
Sawada T et al.	2000–2008 (9)	160	NS	11.3 % (18/160)	>2	1	2011
Fujita N et al.	1992–2003 (12)	280	44.6 % (125/280)	23.9 %	NS	0	2011
Giuliante F et al.	1992–2008 (17)	588	NS	23.1 % (100/433)	≤3	0	2012
Takeishi K et al.	1987–2007 (21)	259	39.8 % (103/259)	33.6 % (87/259)	NS	0	2011
Shimada S et al.	1990–2010 (21)	811	28.1 % (228/811)	34.5 % (280/811)	NS	0	2013
Kim JM et al.	2006–2010 (5)	1139	NS	13.4 % (153/1139)	NS	0	2013
Shirabe K et al.	2004–2007 (4)	46	26.1 % (12/46)	NS	≤5	1	2009
Ohashi M et al.	2006–2007 (2)	78	27.5 % (19/69)	NS	NS	0	2009
Shimada M et al.	1985–1999 (15)	404	36.9 % (149/404)	41.6 % (168/404)	NS	1	2001
Shimada M et al.	1985–1999 (15)	174	23 % (40/174)	34.5 % (59/171)	≤3	1	2001
Utsunomiya T et al.	1990–1998 (9)	116	15.5 % (18/116)	NS	≤3	0	1999
Utsunomiya T et al.	1990–1998 (9)	82	18.3 % (15/82)	NS	≤3	1	1999
Yamamoto M et al.	1985–1994 (10)	186	12.4 % (23/186)	10.2 % (19/186)	≤2	0	2004
Sumie S et al.	1995–2005 (11)	110	NS	15.5 % (17/110)	≤5	0	2008

MPVI Microscopic portal vein involvement; including portal vein invasion and tumor thrombus, *MIM* Microscopic intrahepatic metastases, *NS* Non Specified

Single nodule: 1 yes; 0 no

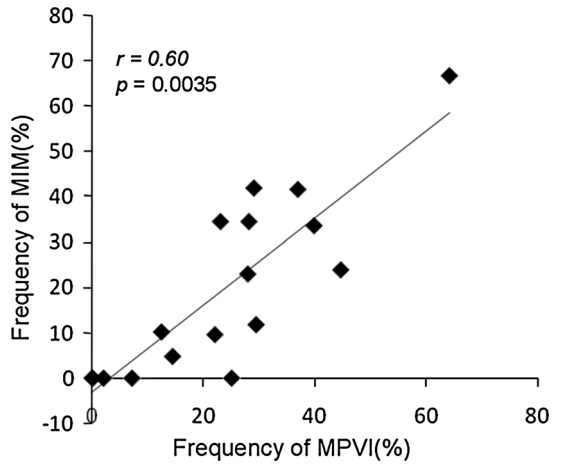

Fig. 1 Scatter plot of microscopic portal vein involvement (MPVI) and intrahepatic metastases (MIM). MPVI was significantly correlated with MIM with coefficient (r) of 0.60 according to Spearman's correlation coefficient analysis ($p = 0.0035$)

no significance between single nodule or multi nodules ($p = 0.156$). Frequency of MIM in resected specimens with single nodule of each series was (18.8 ± 16.6) %, ranging from 0–66.7 %, however, frequency of MIM in resected specimens with multi nodules of each series was (23.1 ± 15.7) %, ranging from 0–62.9 %, and there was no significance between single nodule or multi nodules ($p = 0.363$).

Then data was stratified by tumor size and all tumors were with single nodule (Table 2). It was obvious that early HCC was with very low frequency of MPVI and MIM, almost with frequency of 0. ANOVA result showed that there were no significant difference between groups of tumor ≤2, ≤3, and ≤5 cm, however, group of tumor >5 cm showed significantly higher frequency.

Dynamic evidences of radiology and cytology

There were 3 literatures regarding radiology about relation between tumor and surrounding vessels. Nakashima T. firstly proposed that using barium infusion in HCC, arterial branches acted as afferent vessels, and capillarized sinusoids and portal branches as efferent channels, almost all intrahepatic metastases should result from portal vein invasion of HCC in 1976 [69].Okamoto E.et al. [22] in 1987 reported that in 15 resected HCC specimens, barium sulfate solution was injected directly into the tumor, in 12 cirrhotic specimens, the portal branches were clearly visualized, while hepatic vein branches were not or only faintly stained, the frequency was 80 % (12/15). In 1996, Toyosaka A. also injected radiopaque media to HCC of 23 specimens, in which 74 % (17/23) showed fully visualized portal branches, while hepatic vein branches were not filled

Table 2 Frequencies of MPVI and MIM of single nodule stratified by tumor size in resected specimens

Tumor size (cm)	Frequency of MPVI (%)	Frequency of MIM (%)
≤1.5	0.5 ± 1 (95 cases/4 series)	0 ± 0 (110 cases/5 series)
≤2	16.2 ± 8.4 (177 cases/3 series)	13.9 ± 6.4(359 cases/5 series)
≤3	26.4 ± 12.5 (658 cases/6 series)	28.1 ± 14.1 (445 cases/4 series)
≤5	17.4 ± 7.6 (500 cases/3 series)	18.9 ± 11.7 (1136 cases/6 series)
>5	64.1 (39 cases/1 series)	66.7(39 cases/1 series)

MPVI Microscopic portal vein involvement; including portal vein invasion and tumor thrombus, *MIM* Microscopic intrahepatic metastases

at all. In the remaining 26 %, both portal and hepatic vein branches were opacified, but the portal vein branch was always filled more predominantly [70].

There were 2 literatures regarding cytology about relation between tumor and surrounding vessels. In 1990, Yamamoto M. et al. [71] reported that saline solution was injected into the hepatic artery of 27 livers with HCC, samples were collected through the portal and the hepatic vein. HCC cells were detected significantly in 14.8 % (4/27) from the portal vein, 5.3 % (1/19) from the hepatic vein were not significantly detected, tumors >5 cm in diameter showed a tendency of flowing HCC cells into portal vein. In 1992, Yamanaka N.et al. [32] reported that blood samples were taken from portal veins of 31 HCC patients receiving hepatic resection, which were then stained and screened for HCC cells, the total recovery rate of HCC cells was 22.58 % (7/31). Recovery rate of HCC cells was 0 for tumor ≤5 cm, 38 % for tumor ≤10 cm but >5 cm, and 80 % for tumor >10 cm.

Discussion

Anatomic resection is the removal of liver segment confined by tumor-bearing portal tributaries, whereas nonanatomic resection is the removal of the tumor with adequate margin. Anatomic resection became intact and popular, especially in Japan since 1981 when Makuuchi M. [72] proposed systematic sub-segmentectomy and blue dye injection into the relating feeding portal vein to confirm the portal tributaries that lack landmarks on the surface of liver, however, the superiority of anatomic or nonanatomic resection remains controversial.

It is necessary to reappraise evidences of HCC cells involving the portal vein which is one supportive point of anatomic resection, because HCC can be diagnosed earlier nowadays, the frequency of HCC cells invading the portal vein microscopically may be different from that reported in 1980s and 1990s, especially when considering the size of tumor.

In the total 409 literatures, there are many studies only focusing on microvascular invasion or micrometastasis, rather than MPVI or MIM, because it is difficult to distinguish intracapsular portal vein from hepatic vein; such literatures were excluded in current research. The accurate intracapsular portal vein involvement remains a limitation of current research because the consensus of histological criteria of identifying intracapsular portal vein involvement has not yet been established [64].

MIM can be consequence of spread of tumor through portal invasion [7, 42], which was also demonstrated in current research that MPVI was significantly correlated with MIM. MIM was also observed in current research. 89.2 % of included series in current research were consecutive, with average 12.3 years and 169.5 cases for each series, which can contribute to less bias from literatures. The average frequency of MPVI in resected specimens was 26.4 and 21.5 % for frequency of MIM from overall 65 series, and we only encountered 3 frequencies of MPVI and 1 frequency of MIM, which were more than 50 %. It seems not so frequent when compared to the top 73 % [12].

Gross type, tumor size, tumor number, and tumor differentiation were tumor characteristics, which can be prognostic factors. The frequencies of MPVI and MIM were stratified by tumor size and tumor number in current research. Although there were no significant differences of frequencies of MPVI and MIM between single nodule and multi nodule HCC, frequencies of MPVI and MIM of HCC with single nodule were lower than that of HCC with multi nodules.

It was reported that early HCC was with significant smaller size (usually no more than 1.5 cm) when compared to other types of HCC [39].There were 5 series with such kind of early HCC that were all single nodule HCC. These series were included to stratification of HCC ≤1.5 cm. It was obvious that early HCC was with extremely low frequencies of MPVI and MIM, almost with no MPVI and MIM. For those single nodule HCC ≤2, ≤3, ≤5, and >5 cm, frequencies of MPVI and MIM of single nodule HCC >5 cm were the significantly highest, however, frequencies of MPVI and MIM between single nodule HCC ≤2, ≤3, and ≤5 cm were not significantly different.

Radiology and cytology of dynamic evidences also revealed that portal vein acted as efferent vessel for HCC, which maybe the reason that there was higher frequency of portal vein involvement than hepatic vein involvement. HCC >5 cm showed a tendency of flowing HCC cells into portal vein, which was coincident with significantly high frequency (64.1 %) of MPVI for HCC >5 cm.

There were several limitations in current research besides unclear accurate intracapsular portal vein involvement. Data were not stratified by gross type and tumor differentiation which were important characteristics as tumor size and tumor number. Furthermore, case number and patient inclusion criteria of each consecutive series varied, which could be negative to homogenous and veracity of current research.

Conclusion

In conclusion, the frequency of MPVI of single nodule HCC was lower than that of multi nodule HCC. For single nodule HCC >5 cm, the frequency (64.1 %) of MPVI was significantly high, which needs anatomic resection and the root of portal vein should be firstly ligated because of tendency of flowing HCC cells into portal vein. For single nodule HCC ≤2 cm, there was a risk of about 16.2 % of MPVI, and a risk of about 16.2–26.4 % of MPVI for those single nodule HCC ≤5 cm, however, there was a risk of extremely low to 0 of MPVI for early HCC (≤1.5 cm). Surgeons have to balance liver reserve and risk of MPVI for HCC ≤5 cm before deciding anatomic or nonanatomic resection.

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Conflict of interest There is no conflict of interest to disclose.

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